D1a.

Equiv
DE-A-3402878

PATENT NO EP(UK) 0150792

TRANSLATION OF EUROPEAN PATENT (UK) UNDER SECTION 77(6) (a)

Date of Publication of the Translation 20.2.91

For official use

Your reference
PJC/RAL/LPS EPT 4652

otes
ease type, or write in dark ink using
APITAL letters.

prescribed fee is payable with this
rm. For details, please contact the
tent Office (telephone
1–829 6910).

ragraph 1 of Schedule 4 to the
tents Rules 1990 governs the
mpletion and filing of this form.

his form must be filed in duplicate
d must be accompanied by a
nslation into English, in duplicate.

the whole description
those claims appropriate to the UK
(in the language of the
proceedings)
cluding all drawings, whether or not
ese contain any textual matter but
cluding the front page which
ntains bibliographic information.
e translation must be verified to the
tisfaction of the Comptroller as
rresponding to the original text.

The Patent Office

Filing of translation of European Patent (UK) under Section 77(6)(a)

Form 54/77 Patents Act 1977

(10) European Patent number

1 Please give the European Patent number: 0 150 792

(73) Proprietor's details

2 Please give the full name(s) and address(es) of the proprietor(s) of the European Patent (UK):

Name Algina Aktiengesellschaft

Address c/o Rensch Treuhand Baarer Strasse 43
CH-6301 Zug
SWITZERLAND

Postcode

ADP number
(if known):

(45) European Patent Bulletin date

3 Please give the date on which the mention of the grant of the European Patent (UK) was published in the European Patent Bulletin or, if it has not yet been published, the date on which it will be published:

Date 23.01.91

day month year

Please turn over

PATENTS ACT 1977

AND

PATENTS (AMENDMENT) RULES 1987

I, F.W.J. Humphries, translator to Messrs. Taylor & Meyer, of 29 Kingsmead Road, London SW2 3HY, declare that I am conversant with the German and English languages and that to the best of my knowledge and belief the accompanying text is a true translation of the text on which the European Patent Office has granted or intends to grant European Patent No. 0 150 792 in the name of Algina Aktiengesellschaft

Signed this twenty first day of November 1990

F.W.J. Humphries

The invention relates to a drug for treatment of hyperphosphataemia in chronic uraemia and for treatment of dialysis patients and for prevention of kidney stones, more particularly phosphate-containing and oxalate-containing kidney stones.

The invention also relates to use of calcium and/or magnesium compounds soluble with difficulty for producing a drug for counteracting hyperphosphataemia and prevention of kidney stones.

In the Federal Republic of Germany there are at present about 5,000 patients with chronic uraemia (= renal insufficiency) and about 15,000 patients whose uraemia is so advanced as to require detoxification of the blood by artificial kidneys, i.e. dialysis treatment. Up to three times a week, for three to six hours, these patients have to undergo detoxification of the blood by one of the known methods such as haemodialysis, haemofiltration, peritoneal dialysis or continuous out-patient peritoneal dialysis, in order to remove uraemic toxins such as urea, uric acid, creatinine etc., potassium or phosphate from the organism, i.e. from the blood.

Even after additional dietetic steps such as dietetic limitation of ingestion of phosphate through food, the phosphate level in most patients is still too high after detoxification of the blood. Hyperphosphataemia is an important factor in the pathogenesis of secondary hyperparathyroidism and in the development of renal osteopathy during chronic dialysis treatment. In addition, nearly all uraemic patients are ordered additional medication for lowering the excessive phosphate level to the normal range.

In recent years, aluminium hydroxides such as Aludrox®, antiphosphate or aluminium hydroxycarbonates have been the main substances used for intestinal phosphate bonding and for lowering excessive levels of phosphate in the serum. Up to 10 g or more of the drug are administered per day [M.S. Kaye, Arch. Intern. Med. 124, 553 (1969)]. DE-OS 25 18 083 describes another aluminium salt for reducing the resorption of phosphate.

These known phosphate-bonding substances, however, have disadvantages. In the stomach medium, aluminium hydroxide or aluminium hydroxide carbonate is partly dissolved to form aluminium hydroxide chloride and aluminium chloride, thus liberating $Al^{3\oplus}$, which is resorbed in the stomach, particularly in the upper small intestine, and via the blood enters the bones and other parts of the body and, after a number of years, can cause serious diseases such as dialysis encephalopathy or osteomalacia with a tendency to spontaneous fractures, anaemia, etc. [A.C. Alfrey et al, Trans. Am. Soc. Artif. Int. Org. 18, 257 (1972); A.C. Alfrey et al, Kidney Interna. 18, 115 (1980), J.T. McCall et al, Kidney Intern. 18, 115 (1980)]. According to the statistics, 10 to 12% of dialysis patients die from cerebral incidents, and quite a few from dialysis encephalopathy [H. Pogglitsch, Nieren und Hochdruckkrankheiten (= Kidneys and diseases accompanied by hypertension) 10, 210 (1981)].

Even if aluminium hydroxide is administered in a form resistant to gastric juices but soluble in the small intestine, the result as before is undesired resorption of aluminium [H. Pogglitsch et al, Nieren und Hockdruckkrankheiten, 12, 186 (1983)]. It therefore appears necessary to discontinue the phosphate-bonding preparations containing aluminium, as used at present.

In addition to aluminium-containing preparations, calcium carbonate is used in individual cases for lowering of phosphates. Calcium carbonate dissolves in the acid medium of the stomach, whereupon phosphate in the form of insoluble calcium phosphate can be bonded in the neutral medium of the small intestine and excreted with the faeces. This treatment, however, presents serious problems, i.e. increased intake of calcium into the blood, the final result being acute and possibly fatal hypercalciaemia. Consequently, treatment with calcium carbonate has not hitherto been generally accepted.

Kidney stones containing phosphate can also be formed by intake of phosphate in food, the main products being calcium phosphate stones. Recurrence of phosphate-containing kidney stones is likewise prevented by using aluminium-containing phosphate bonding agents, with the previously-mentioned disadvantages.

Similarly, intake of food containing or rich in oxalate promotes the formation of oxalate-containing kidney stones.

FR-A-4 265 M (see Résumé, paragraphs 3 and 4) describes drugs resistant to gastric juices and containing either magnesium hydroxide or magnesium oxide as the main constituent.

Martindale (The Extra Pharmacopoeia), 28th edition 1982, pages 82 and 83 and particularly 699-t, describes the use of magnesium hydroxide and light magnesium oxide as a drug. This citation contains no hint that certain calcium compounds can be used for treatment of hyperphosphateemia and prevention of phosphate-containing and/or oxalate-containing kidney stones.

The object of the invention is to provide a drug for reducing the intake of phosphate, particularly in chronic uraemia and in dialysis patients, and thus lowering the phosphate level in the serum. A particuler aim of the invention is to provide drugs for preventing the formation of phosphate-containing and/or oxalate-containing kidney stones. The drug is more particularly for patients known to have a tendency towards the formation of kidney stones. The drug should be free from the disadvantages of commercially obtainable substances.

Another aim of the invention is to use calcium and/or magnesium compounds soluble with difficulty for producing a drug having a new indication.

The invention relates to a drug for treatment of hyperphosphataemia and prevention of phosphate-containing and/or oxalate-containing kidney stones, characterised in that it contains a calcium compound which is soluble with difficulty at pH 6 - 9, i.e. calcium carbonate, calcium hydroxide, calcium oxide and/or calcium sulphate, together if required with conventional excipients and/or diluents in a form resistant to gastric juices.

The invention also relates to use of at least one calcium and/or magnesium compound which is soluble with difficulty at pH 6 - 9 for producing a drug in a form resistant to gastric juices, for treatment of hyperphosphataemia and for prevention of phosphate-containing and/or oxalate-containing kidney stones.

The invention also relates to use of

i) Calcium carbonate for producing a drug in a form resistant to gastric juices for counteracting hyperphosphataemia and for treatment of phosphate-containing kidney stones,

ii) Magnesium carbonate, magnesium hydroxide carbonate, magnesium hydroxide and magnesium oxide for producing a drug in a form resistant to gastric juices for treatment of oxalate-containing kidney stones, and

iii) Calcium and magnesium compounds which are soluble with difficulty at pH 6 - 9 in combination for producing a drug in a form resistant to gastric juices for counteracting oxalate-containing kidney stones.

It has surprisingly been found that when calcium and/or magnesium compounds soluble with difficulty at pH 6 - 9 are prescribed, phosphates or oxalates are effectively bonded in the form of insoluble calcium phosphate or calcium oxalate or magnesium phosphate or magnesium oxalate without excessive undesirable resorption of calcium or magnesium cations in the blood, as occurs e.g. on administration of soluble calcium or magnesium salts, e.g. citrates or carbonates, which dissolve in the stomach.

It has also surprisingly been found that the desired effect is obtained if the calcium and magnesium compounds are used in the form of a drug resistant to gastric juices.

A critical feature of the invention is that the drug is administered in a form resistant to gastric juices. This form of administration, completely surprisingly and unexpectedly, can be used to bond phosphate or oxalate without excessive interfering resorption of calcium or

magnesium into the blood, as in the case of the prior-art form of administration of these calcium or magnesium compounds.

The drug form resistant to gastric juices releases the calcium or magnesium compound soluble with at pH 5 - 8 into the small intestine, where it slowly reacts with the phosphate and/or oxalate in the small intestine to form insoluble calcium phosphates and calcium oxalates or magnesium phosphates and magnesium oxalates. These substances are then excreted in the faeces without resorption.

Since the drug, e.g. calcium or magnesium carbonate, is soluble with difficulty at the pH of 6 to 8 prevailing in the small intestine, there is no excessive resorption of calcium or magnesium ions, in contrast to administration in the conventional form of a drug which is soluble in gastric juices.

In the drug and use according to the invention, use is made of calcium and/or magnesium compounds which are soluble with difficulty at a pH from 6 to 9, preferably from 6.5 to 8. Examples of such substances are calcium carbonate, calcium hydroxide, calcium oxide, calcium sulphate, magnesium carbonate, magnesium hydroxide carbonate, magnesium oxide and magnesium hydroxide. Of course, mixtures of at leest two or more of these compounds can also be used.

Preferably according to the invention, calcium carbonate is used for treatment of hyperphosphataemia and phosphate-containing kidney stones. Preferably also, the magnesium compounds, preferably magnesium carbonate, magnesium hydroxide carbonate, magnesium hydroxide and magnesium oxide

or mixtures thereof, are used for treetment of oxalate-containing kidney stones. Mixtures of the eforementioned calcium and magnesium compounds are also suitable for treatment of oxalate-containing kidney stones.

If required, the calcium and magnesium compounds can be used together with conventional drug excipients and diluents and in the form of a drug resistant to gastric juices. The drugs can in known manner be in the form of tablets or hard gelatin capsules or soft gelatin capsules or granulates, all resistant to gastric juices. The compounds can also be in depot form resistant to gastric juices, so that only one dose per day is required.

The calcium and magnesium compounds present in the drugs according to the invention and used according to the invention are commercially obtainable. They can be used in the form of powders, granulates, beads or the like for producing the drugs according to the invention. The powders can be fine or coarse.

The amount of phosphate bonded is e.g. ebout 40 to 180 mg/g for calcium carbonate in vitro, and about 100 to 300 mg/g for calcium sulphate, and is therefore higher than for many aluminium hydroxides.

The oxalate bonding is about 50 to 200 mg oxalate/g for calcium carbonate and about 100 to 250 mg oxalate/g for calcium sulphate. The values meesured for magnesium compounds are similar.

It was surprising and not obvious that the phosphate-bonding capecity of calcium and magnesium compounds is of the same

order, and sometimes higher, than that of aluminium hydroxide.

The following examples explain the invention. In the examples, the following methods of determination were used:

a) Determination of $HPO_4^{2\ominus}$

$HPO_4^{2\ominus}$ was photometrically determined by the method of Gomorri [G. Gomorri, J. Leb. Clin. Med. 27, 955 (1942)]. In the process, inorganic phosphate combines with sodium molybdate to form phosphorus molybdate, which is reduced with p-methylaminophenol sulphate and converted to colloidal molybdenum blue, which is photometrically determined.

b) Determination of oxalate

Oxalate was titrimetrically determined by means of a 0.02 potassium permanganate test solution, which was stabilized by boiling for one hour. 10 ml of the sample was mixed with 150 ml twice-distilled water and 10 ml of 1 + 4 dilute concentrated sulphuric acid, heated to 75 - 85°C and titrated with the $KMnO_4$ solution until permanently faint pink.

Example 1

Tablets or hard gelatin capsules resistent to gastric juices and each containing 500 mg of the drug were manufactured in known manner.

The pH was adjusted to the desired value with Tris buffer, caustic soda solution and an excess of K_2HPO_4, and the tablets or hard gelatin capsules were added and incubated

for one hour. The free phosphate was then determined, thus determining the phosphate-bonding capacity.

The results were as follows:

Calcium carbonate tablets

pH = 7	phosphate bonding:	120 mg/g
pH = 7.5	phosphate bonding:	135 mg/g
pH = 8.0	phosphate bonding:	160 mg/g

Calcium carbonate (hard gelatin capsule)

pH = 7.0	phosphate bonding:	125 mg/g
pH = 7.5	phosphate bonding:	140 mg/g
pH = 8.0	phosphate bonding:	170 mg/g

Calcium sulphate . $2H_2O$ (tablets)

pH = 7.0	phosphate bonding:	280 mg/g
pH = 7.5	phosphate bonding:	300 mg/g
pH = 8.0	phosphate bonding:	300 mg/g

Magnesium carbonate (tablet)

pH = 7.0	phosphate bonding:	140 mg/g
pH = 7.5	phosphate bonding:	150 mg/g
pH = 8.0	phosphate bonding:	150 mg/g

Magnesium oxide (hard gelatin capsules)

pH = 7.0	phosphate bonding:	160 mg/g
pH = 7.5	phosphate bonding:	160 mg/g
pH = 8.0	phosphate bonding:	180 mg/g

Under the same conditions, the phosphate bonding by aluminium hydroxide (Aludrox® tablet) was 170 mg/g.

Example 2

In order to determine the oxalate bonding capacity, two series of samples were prepared:

a) 500 mg oxalic acid in 190 ml of 0.1 M Tris-HCl and

b) 500 mg oxalic acid and 960 mg K_2HPO_4 in 190 ml 0.1 M Tris-HCL

In order to simulate the pH conditions in the individual sections of the intestine, in each series samples were prepared with the following pH values:

pH = 6.0; 6.5; 7.0; 7.5; 8.0

After the pH had been exactly adjusted with NaOH or HCl, the buffer was made up to 200 ml and two tablets resistant to gastric juices (containing 500 mg of the drug) or hard gelatin capsules resistant to gastric juices (containing 500 mg of active principle) or soft-gelatin capsules resistant to gastric juices, (containing 500 mg active principle) were added to each sample.

After the pH had been accurately adjusted with NaOH and HCl, the buffer was made up to 200 ml. The starting materials were incubated with slight agitation at 37°C in a water bath and 12-ml portions were removed every six minutes and any calcium oxalate or magnesium oxalate formed was separated by centrifuging and 10-ml portions of the supernatant were titrated with $KMnO_4$ solution (see methods of determination).

Results:

Calcium carbonate (tablets, resistant to gastric juices)

pH	Bonding of oxalate (mg/g)
6.0	a) 180 mg b) 150 mg
6.5	a) 170 mg b) 145 mg
7.0	a) 165 mg b) 145 mg
7.5	a) 165 mg b) 140 mg
8.0	a) 165 mg b) 140 mg

Calcium oxide (soft gelatin capsules, resistant to gastric juice)

pH	Bonding of oxalate (mg/g)
6.0	a) 150 mg b) 130 mg
6.5	a) 160 mg b) 140 mg
7.0	a) 160 mg b) 140 mg
7.5	a) 165 mg b) 140 mg
8.0	a) 170 mg b) 150 mg

Magnesium carbonate (tablets resistant to gastric juices)

pH	Bonding of oxalate (mg/g)
6.0	a) 190 mg b) 150 mg
7.0	a) 200 mg b) 150 mg
8.0	a) 220 mg b) 160 mg

Magnesium hydroxide carbonate (hard gelatin capsules resistant to gastric juice)

pH	Bonding of oxalate (mg/g)
6.0	a) 180 mg b) 140 mg
6.5	a) 180 mg b) 150 mg
7.0	a) 200 mg b) 160 mg
8.0	a) 210 mg b) 180 mg

Claims for the contracting states DE, GB, FR, NL, IT, BE, SE and CH/LI

1. A drug for treatment of hyperphosphataemia and prevention of phosphate-containing and/or oxalate-containing kidney stones, characterised in that it contains a calcium compound which is soluble with difficulty at pH 6 - 9, i.e. calcium carbonate, calcium hydroxide, calcium oxide and/or calcium sulphate, together if required with conventional excipients and/or diluents in a form resistant to gastric juices.

2. A drug according to claim 1, characterised in that it is in the form of tablets or hard gelatin capsules or soft gelatin capsules or a granulate, all resistant to gastric juices.

3. Use of at least one calcium and/or magnesium compound which is soluble with difficulty at pH 6 - 9 for producing a drug in a form resistant to gastric juices, for treatment of hyperphosphataemia and for counteracting phosphate-containing and/or oxalate-containing kidney stones.

4. Use according to claim 3, characterised in that calcium carbonate, calcium hydroxide, calcium oxide and/or calcium sulphate is used as the calcium compound which is soluble with difficulty at a pH from 6 to 9.

5. Use according to claim 3, characterised in that magnesium carbonate, magnesium hydroxide carbonate, magnesium hydroxide and/or magnesium oxide is used as the magnesium compound which is soluble with difficulty at a pH from 6 to 9.

6. Use of calcium carbonate for producing a drug in a form resistant to gastric juices and for treatment of hyperphosphataemia and treatment of phosphate-containing kidney stones.

7. Use of magnesium carbonate, magnesium hydroxide carbonate, magnesium hydroxide and/or magnesium oxide for producing a drug in a form resistant to gastric juices and for treatment of oxalate-containing kidney stones.

8. Use of calcium and magnesium compounds which are soluble with difficulty at a pH from 6 to 9 in combination for producing a drug in a form resistant to gastric juices and for counteracting of oxalate-containing kidney stones.

Claims for the contracting stete AT

1. A method of producing a drug for treatment of hyperphosphataemia and for prevention of phosphate-containing and/or oxalate-containing kidney stones, characterised in that a calcium compound soluble with difficulty at a pH from 6 to 9, i.e. calcium carbonate, calcium hydroxide, calcium oxide and/or calcium sulphate is mixed with conventionel excipients and/or diluents and the mixture is converted in known manner into a form of drug resistant to gastric juices.

2. A method according to claim 1, characterised in that the drug is produced in the form of tablets or hard gelatin capsules or soft gelatin capsules or a granulate, all resistant to gastric juices.

3. Use of at least one calcium and/or magnesium compound which is soluble with difficulty at pH 6 - 9 for producing a drug in a form resistant to gastric juices, for treatment of hyperphosphataemia and for counteracting phosphate-containing and/or oxalate-containing kidney stones.

4. Use according to claim 3, characterised in that calcium carbonate, calcium hydroxide, calcium oxide and/or calcium sulphate is used as the calcium compound which is soluble with difficulty at a pH from 6 to 9.

5. Use according to claim 3, characterised in that magnesium carbonate, magnesium hydroxide carbonete, magnesium hydroxide and/or megnesium oxide is used as the magnesium compound which is soluble with difficulty at a pH from 6 to 9.

6. Use of calcium carbonate for producing a drug in a form resistant to gastric juices and for treatment of hyperphosphataemia and treatment of phosphate-containing kidney stones.

7. Use of magnesium carbonate, magnesium hydroxide carbonate, magnesium hydroxide and/or magnesium oxide for producing a drug in a form resistant to gastric juices and for treatment of oxalate-containing kidney stones.

8. Use of calcium and magnesium compounds which are soluble with difficulty at a pH from 6 to 9 in combination for producing a drug in a form resistant to gastric juices and for counteracting oxalate-containing kidney stones.